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Effects of Dopexamine on Lipid Peroxidation During Aortic Surgery in Pigs: Comparison with Dopamine

G. Kostopanagiotou,[1]* A. Pandazi,[1] I. Andreadou,[1] A. Doufas,[2] I. Chondroudaki,[1] T. Kotsis,[2] D. Rizos,[2] C. Costopanagiotou[1] and V. Smyrniotis[2]

2nd Departments of [1]Anaesthesiology, School of Medicine, Attikon Hospital, University of Athens, 1 Rimini Str., Chaidari, GR-12462 Athens, and [2]Surgery, School of Medicine, Aretaieion Hospital, University of Athens, 76 Vas. Sofias Ave, GR-11528 Athens, Greece

Objective. *We investigated the dose-related effect of dopexamine and dopamine on free radical production and lipid peroxidation estimated by MDA measurements in an ischaemia-reperfusion model of supraceliac aortic repair.*
Design. *Prospective, randomized, blinded experimental study.*
Materials. *Twenty-five healthy pigs.*
Methods. *All experiments were performed under general endotracheal anaesthesia. Supraceliac aortic cross clamping was performed in all pigs. The pigs were randomly assigned into five groups (*n*=5 in each group) and received a continuous intravenous infusion of normal saline (CTL), dopamine 2 μg kg^{-1} min^{-1} (dopa 2), dopamine 8 μg kg^{-1} min^{-1} (dopa 8), dopexamine 2 μg kg^{-1} min^{-1} (dopex 2), dopexamine 8 μg kg^{-1} min^{-1} (dopex 8). Cardiac output, mean arterial pressure, arterial blood gas analysis and blood sampling for plasma MDA measurements (to reveal lipid peroxidation) were recorded after induction of anaesthesia (baseline), 60 and 120 min after cross-clamping of aorta (ischaemia phase), and 60 and 120 min after restoration of flow (reperfusion phase).*
Results. *Dopexamine and dopamine at 8 μg kg^{-1} min^{-1} reduced MDA at 60 and 120 min after reperfusion.*
Conclusion. *Dopexamine seems superior to dopamine in reducing oxygen free radicals and subsequent lipid peroxidation during reperfusion after supraceliac aortic cross clamping in pigs.*

Keywords: Aortic surgery; Dopexamine; Dopamine; MDA; Lipid peroxidation; Oxygen free radicals.

Aortic aneurysm repair surgery or surgery during trauma resuscitation involves cross clamping of the abdominal aorta for the open surgical reconstruction of the diseased aorta. Damage that occurs after such temporary interruption of blood flow to tissue is commonly believed to be due to a combination of injury suffered during the ischaemic interval from metabolic deterioration and injury caused by transient generation of oxygen free radicals produced at reperfusion.[1,2] The pathophysiology that produces damage from free radicals is complex and involves several types of lipid peroxidation and damage to proteins or DNA.[2] The determination of malondialdehyde plasma concentration (MDA) has been a valuable method to reveal *in vivo* lipid peroxidation.[3,4]

The effects of dopamine and dopexamine on haemodynamics and visceral ischaemia during operations involving aortic cross-clamping have been previously examined.[5–8] Furthermore, some investigators suggest that dopexamine used in experimental models can prevent lipid peroxidation induced by oxygen free radicals.[9,10] Antioxidant activity on the other hand, has been attributed to cabergoline, a dopamine agonist, administered in Parkinsons disease.[11]

The present experimental study in pigs deals with the dose-related effect of dopexamine and dopamine on free radical production and subsequent lipid peroxidation estimated by MDA measurements during an ischemia-reperfusion model of supraceliac aortic repair.

Materials and Methods

Twenty-five healthy pigs [BW 22 (2.5) kg, mean (SD)] were used in the study. All animals received care in compliance with the 'Principles of Laboratory Animal

*Corresponding author. Dr. Georgia Kostopanagiotou, MD, PhD, 44 Danais Str., Patima Chalandriou, 15 238 Athens, Greece.
E-mail address: banesthclin@attikonhospital.gr

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Care', formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals, prepared by the Academy of Sciences and published by the National Institutes of Health (Institute of Laboratory Animal Resources Commission on Life Sciences, 1996). This prospective, randomized study was approved by the local Scientific Committee of Aretaeion Hospital. Animals were randomly assigned to study groups via blind-envelope method.

Animals were fasted overnight with free access to water before the experiments. All experiments were performed under general endotracheal anaesthesia by the same team and the conditions were carefully kept identical, particularly the anaesthetic (including fluid and drug administration) and surgical steps. On the morning of the procedure ketamine, midazolam and atropine, at 15, 0.5 and 0.05 mg kg^{-1}, respectively, were administered IM. Anaesthesia was induced with 5 mg kg^{-1} of sodium thiopental IV and intubation of the trachea was performed by a 6.0 mm cuffed tracheal tube. Anaesthesia and analgesia were maintained with isoflurane 0.5–1.5% and continuous intravenous infusion of fentanyl at a rate of 5–10 μg kg^{-1} h^{-1}. A continuous intravenous infusion of pancuronium bromide (0.2 mg kg^{-1} h^{-1}) was used for maintenance of neuromuscular blockade. Animals' lungs were ventilated with tidal volumes of 8–10 ml kg^{-1} at a frequency of 15–25 breaths/min (Model Sulla 808V, Drager, Lubeck, Germany) by an air/oxygen mixture (FiO_2 0.4). End-tidal CO_2 was measured with a sidestream infrared CO_2 monitor (CD-102 Normocap, Datex Inc., Helsinki, Finland) to document adequate ventilatory patterns (ET CO_2 at 32–42 mmHg). The temperature was monitored using the Swan-Ganz's thermistor electrode and kept at 37 (0.5) °C using a heating pad. After induction of anaesthesia, a 20G arterial catheter (Hydrocath™ Arterial Catheter Kit Seldinger Technique, Becton Dickinson Critical Care Systems, Singapore), was inserted in the exposed right carotid artery for continuous arterial pressure monitoring and blood sampling, a 18G vein catheter (Helm Pharmaceuticals GMBH, Hamburg, Germany) was introduced in the right external jugular vein for fluid and drug administration and a second sheath (6 Fr) in the internal jugular vein for the advance of a Swan-Ganz catheter (5.5 F, Abbott, Critical Care Systems, Abbot Laboratories, N. Chicago, IL, USA). The monitoring (Criticon, Dinamap™ Plus, Vital Signs Monitors, Tampa, FL, USA) included continuous measurement of systemic arterial blood pressure, pulse oximetry (SpO_2), capnography (ET CO_2), right atrial and pulmonary arterial pressures. Cardiac output measurements using the thermodilution method via the Swan-Ganz catheter, arterial blood gas analysis and blood sampling for plasma MDA measurements were performed at the appropriate time points.

Surgical protocol

All animals underwent a midline laparotomy under strict aseptical conditions. The aorta was meticulously prepared and supraceliac aortic cross-clamping was performed. Fluid losses due to surgical procedures were replaced intravenously with Ringer's lactated (5–10 ml kg^{-1} h^{-1}) and a colloid solution (haemacel) was infused to keep the central venous pressure above 4 mmHg. After 120 min of aortic cross-clamping the clamp was released and the pigs were kept under anaesthesia for another 120 min. Isoflurane inhalation, pancuronium and fentanyl infusions were stopped about 30 min before the end of the procedure and neostigmine 1.2 mg with atropine 0.6 mg were administered intravenously to reverse the residual neuromuscular blockade at the end of operation.

Experimental protocol

The pigs were randomly assigned into five groups, according to the study drug that they received:

Control group (CTL, $n=5$). The animals in this group received a continuous intravenous infusion of normal saline.
DOPA 2: ($n=5$). In this group the pigs received a continuous intravenous infusion of dopamine 2 μg kg^{-1} min^{-1}.
DOPA 8: ($n=5$). In this group the pigs received a continuous intravenous infusion of dopamine 8 μg kg^{-1} min^{-1}.
DOPEX 2: ($n=5$). A continuous intravenous infusion of dopexamine 2 μg kg^{-1} min^{-1} was administered in this group.
DOPEX 8: ($n=5$). A continuous intravenous infusion of dopexamine 8 μg kg^{-1} min^{-1} was administered in this group.

Drug infusion was started after anaesthesia induction and stopped at the end of measurement period (120 min after reperfusion).

The parameters were determined and detailed at five time points: After induction of anaesthesia (baseline), 60 and 120 min after cross-clamping of aorta (ischaemia phase), and 60 and 120 min after restoration of flow (reperfusion phase).

Arterial blood samples at the standard time points during the study were analyzed for hemoglobin concentration and arterial blood gases (ABL 300 Radiometer, Copenhagen, Denmark).

Measurement of malondialdehyde

Plasma malondialdehyde concentration was measured at the standard time points during the study, as an index of the occurrence of lipid peroxidation and the development of oxidative stress.[3] MDA concentration was determined spectrophotometrically at 586 nm and expressed as μM. 0.65 ml of 10.3 mM *N*-methyl-2-phenyl-indole in acetonitrile was added to 0.2 ml of plasma. After vortexing for 3–4 s and adding 0.15 ml of HCl 37%, samples were mixed well and closed with a tight stopper and incubated at 45 °C for 60 min. The samples were then cooled on ice, centrifuged and the absorbance was measured spectrophotometrically at 586 nm. A calibration curve of an accurately prepared standard MDA solution (from 2 to 20 nmol ml^{-1}) was also run for quantitation. Measurements of each group was performed in triplicate, and standard deviation was less than $\pm 10\%$. MDA concentrations were expressed as mean $\pm$ SE.[3,4]

Data analysis and statistics

All results are presented as mean $\pm$ standard error (SEM). Haemodynamic data were analysed using two way analysis of variance. Comparisons of absolute values of variables among the five groups were analyzed by one way analysis of variance. Pairwise multiple comparisons were performed using the Scheffe test. ANOVA was used for the comparison of each variable separately during the treatment period (baseline until 120 min of reperfusion). Pairwise multiple comparisons were performed using the method of Tukey. All changes from baseline of variables are compared among five treatments by means of one way analysis of variance. All tests are two-sided with 95% significance level. Statistical analysis was performed using the statistical package SPSS vr 10.00 (Statistical Package for the Social Sciences).

Results

Effect of dopamine or dopexamine on haemodynamics

Haemodynamic and metabolic data are included in Tables 1–4. Hemoglobin levels did not change significantly (Table 1). Aortic cross-clamping (60 and 120 min of ischaemia) induced a significant increase in MAP compared to baseline in all study groups, except dopex 8 group. MAP in both groups treated with dopexamine was significantly lower compared with the control group at the 60th and 120th min of ischaemia. During reperfusion following declamping (60 and 120 min of reperfusion) MAP decreased in all groups compared to baseline levels, with the larger decrease observed in dopex 8 group (Table 2).

Cardiac output was little altered in the control group and in pigs treated with dopamine both during ischaemia and reperfusion. During the whole study period a higher cardiac output was observed in pigs receiving dopexamine in both doses studied, in comparison with the other groups and baseline values (Table 3). Arterial pH decreased significantly compared to baseline values in all the animals studied both during ischaemia and reperfusion. Animals treated with dopexamine 8 μg kg^{-1} min^{-1} had the lowest pH values (Table 4).

No intra- or post-operative death occurred, and all the animals had an uneventful recovery from anaesthesia at the end of the study.

Effect of dopamine or dopexamine on plasma malondialdehyde concentration

Plasma malondialdehyde concentrations measured at the different time points of the study are presented in

Table 1. Hemoglobin levels

	CTL	DOPA 2	DOPA 8	DOPEX 2	DOPEX 8
Baseline	8 (0.5)	8 (1.5)	8 (1)	7 (1.5)	7.5 (0.5)
+60 min isch	9 (2)	9 (2.5)	9.5 (1)	8 (1.5)	8 (1)
+120 min sch	10.1 (1)	8.6 (1.5)	9.5 (1)	9.5 (2.5)	9.5 (1.5)
+60 min rep	10.3 (1.8)	10.1 (2.3)	9.5 (1)	8.5 (2.5)	9.5 (0.5)
+120 min rep	11.2 (1.8)	9 (3)	10 (0.5)	9.5 (3)	9.5 (1)

Values are expressed as g/dl, mean (SD). Baseline, after induction of anaesthesia, before operation starting; +60 and +120 min isch, after 60 and 120 min of infrarenal aortic cross-clamping, respectively; +60 and +120 min rep, after 60 and 120 min of reperfusion following declamping, respectively.

Table 2. Changes in MAP

	CTL	DOPA 2	DOPA 8	DOPEX 2	DOPEX 8
Baseline	117 (8)	122 (23)	126 (10)	115 (4)	111 (19)
+60 min isch	148 (11)*	156 (7)*	153 (26)*	138 (12)Å,*	103 (18)Å,*
+120 min isch	152 (16)*	141 (13)*	156 (20)*	135 (10)Å,*	100 (8)Å,*
+60 min rep	101 (20)*	104 (29)*	108 (17)*	103 (10)*	92 (6)Å,*
+120 min rep	104 (15)*	107 (29)*	110 (17)*	100 (13)*	86 (12)Å,*

Values are expressed as mmHg, mean (SD). *, $p<0.05$ compared to baseline value; Å, $p<0.05$ compared to the corresponding control group; baseline, after induction of anaesthesia, before operation starting; +60 and +120 min isch, after 60 and 120 min of infrarenal aortic cross-clamping, respectively; +60 and +120 min rep, after 60 and 120 min of reperfusion following declamping, respectively.

Figs. 1 and 2. A significant increase of plasma MDA was observed in the control group at 120 min of aortic cross-clamping (ischaemia phase) and 60 and 120 min after release of aortic clamp (reperfusion phase) compared to baseline values (Figs. 1 and 2). When dopamine was administered in both doses tested, a significant increase in MDA values was obtained at 120 min of ischaemia, but MDA decreased during reperfusion and this decrease was statistically significant compared to the values of the control group in pigs treated with dopamine at the dosage of 8 $\mu g\ kg^{-1}\ min^{-1}$ (Fig. 1). Administration of dopexamine at a dosage of 8 $\mu g\ kg^{-1}\ min^{-1}$ also resulted in a significant increase in MDA levels at 120 min of ischaemia (Fig. 2). Plasma malondialdehyde concentrations after 60 and 120 min of reperfusion were significantly lower compared to values of the control group at the same time points, when dopexamine was used (Fig. 2).

Discussion

In the present study a significant increase in MDA concentration in plasma was observed at the 120th min of ischaemia, as well as at 60th and 120th min of reperfusion in the control group, compared to the baseline, indicating the existence of free radical production that could mediate damage during reperfusion. Dopamine administration at both doses tested and dopexamine at the high dosage tested could not prevent lipid peroxidation during prolonged (120 min) ischaemia. In contrast the MDA values during reperfusion time were decreased after the administration of both agents, indicating an antioxidant effect of these agents. Compared to dopamine, dopexamine resulted in better antioxidant activity, as it lowered significantly the circulating MDA during reperfusion even when administered at the low dosage.

Previous studies have also confirmed the presence of free radicals and lipid peroxidation after ischaemia and reperfusion during artery cross-clamping.[1,2] As far as dopexamine is concerned, there is evidence that several complex mechanisms are involved in its ability to prevent ischaemia-reperfusion induced organ damage. It has been shown that dopexamine was effective in antagonizing the lethal effects of oxygen free radicals generated by the administration of xanthine and xanthine-oxidase given intravenously to anaesthesized rats.[9,12,13] Furthermore, this agent significantly decreased plasma lipid peroxides in free-radical induced respiratory toxicity in rats.[10] Cabergoline, a dopamine agonist, has been found to have synergistic antioxidant activity with vitamin E, when administered to patients with Parkinsons disease.[11]

The antioxidant effects of dopexamine are mediated specifically via adrenergic receptors.[9,12,13] The results of our study indicate that a selective adrenergic receptor agonist (dopexamine) has a better antioxidant effect compared to a non selective adrenergic receptor agonist (dopamine) confirming the above hypothesis that β-2 adrenergic receptors agonists may be involved in the reduction of the oxidative damage of reperfusion injury. The exact mechanism needs to be elucidated.

Table 3. Changes in CO

	CTL	DOPA 2	DOPA 8	DOPEX 2	DOPEX 8
Baseline	3.5 (3)	3.6 (0.5)	3.5 (0.5)	3.8 (1)	3.6 (3)
+60 min isch	3 (2)	3.5 (0.1)	3 (0.5)	5 (2)Å,*	6 (4)Å,*
+120 min isch	3 (1)	3 (1)	3 (1)	5 (1.5)Å,*	5 (1)Å,*
+60 min rep	3.5 (2.5)	3.6 (0.5)	3 (1)	5.5 (0.5)Å,*	6 (1)Å,*
+120 min rep	3 (2)	3.5 (1.5)	3 (1)	4.5 (1)Å,*	6 (0.5)Å,*

Values are expressed as l/min, mean (SD). Å, $p<0.05$ compared to the corresponding control group; baseline, after induction of anaesthesia, before operation starting; +60 and +120 min isch, after 60 and 120 min of infrarenal aortic cross-clamping, respectively; +60 and +120 min rep, after 60 and 120 min of reperfusion following declamping, respectively.

Table 4. Changes in pHart

	CTL	DOPA 2	DOPA 8	DOPEX 2	DOPEX 8
Baseline	7.48 (0.09)	7.48 (0.06)	7.49 (0.07)	7.46 (0.03)	7.48 (0.04)
+60 min isch	7.40 (0.01)*	7.42 (0.02)*	7.41 (0.04)*	7.36 (0.07)*	7.32 (0.05)*,Å
+120 min isch	7.38 (0.03)*	7.43 (0.02)*	7.40 (0.04)*	7.36 (0.06)*	7.31 (0.11)*,Å
+60 min rep	7.37 (0.03)*	7.42 (0.07)*	7.36 (0.08)*	7.38 (0.06)*	7.27 (0.10)*,Å
+120 min rep	7.37 (0.02)*	7.44 (0.05)*	7.40 (0.05)*	7.41 (0.08)*	7.25 (0.07)*,Å

Values are expressed as mmHg, mean (SD). *, $p<0.05$ compared to baseline value; Å, $p<0.05$ compared to the corresponding control group; baseline, after induction of anaesthesia, before operation starting; +60 and +120 min isch, after 60 and 120 min of infrarenal aortic cross-clamping, respectively; +60 and +120 min rep, after 60 and 120 min of reperfusion following declamping, respectively.

The auto-oxidation of catecholamines is unlikely to be a primary source of oxygen radicals in ischaemia-reperfusion injury, since, it is extremely slow at physiological pH.[14,15]

We could not find any other studies investigating the antioxidant role of dopamine or dopexamine in aortic aneurysm repair surgery. However, in patients undergoing hemihepatectomy with temporary total cross-clamping of hepatic inflow, low-dose dopexamine ($0.5\ \mu g\ kg^{-1}\ min^{-1}$) and dopamine ($2.5\ \mu g\ kg^{-1}\ min^{-1}$) had similar hepatoprotective effects.[16]

As far as haemodynamics is concerned, changes observed in our control group are characteristic of those induced during aortic cross-clamping and unclamping.[17] Dopamine at both doses tested does not seem to influence the haemodynamic response during ischaemia and reperfusion. This observation agrees with Studer *et al.*, who administered dopamine at $10\ \mu g\ kg^{-1}\ min^{-1}$ infusion during supraceliac

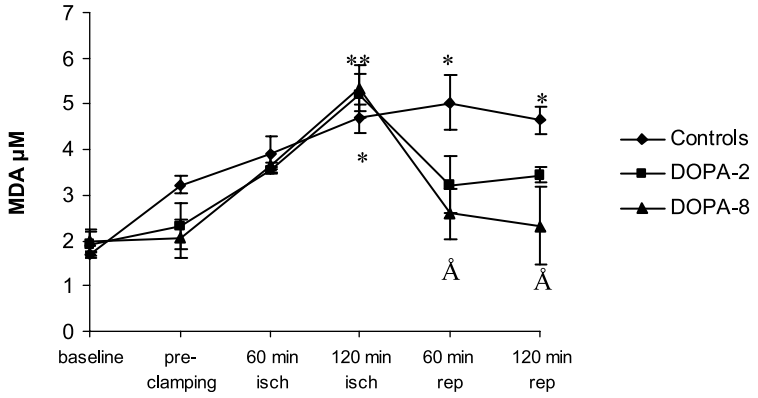

Fig. 1. Malondialdehyde plasma concentrations (MDA) in µM [mean (SE)] at the standard time points in controls (CTL) and in pigs treated with dopamine 2 and 8 $\mu g\ kg^{-1}\ min^{-1}$ (DOPA 2 and DOPA 8 group, respectively). *, $p<0.05$ compared to baseline value; **, $p<0.001$ compared to baseline value; Å, $p<0.05$ compared to the corresponding control group.

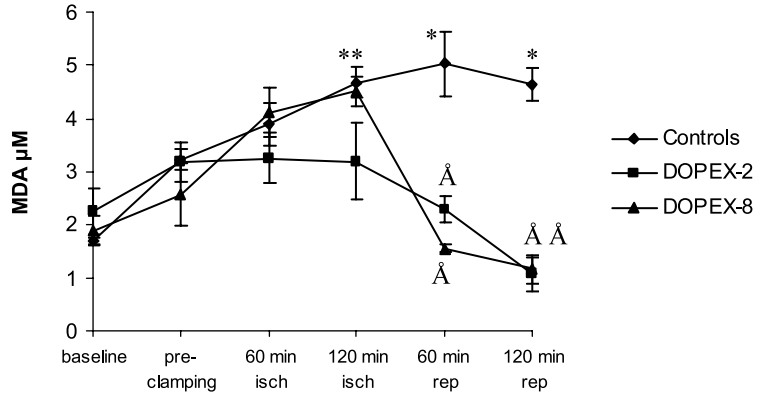

Fig. 2. Malondialdehyde plasma concentrations (MDA) in µM [mean (SE)] at the standard time points in controls (CTL) and in pigs treated with dopexamine 2 and 8 $\mu g\ kg^{-1}\ min^{-1}$ (DOPEX 2 and DOPEX 8 group, respectively). *, $p<0.05$ compared to baseline value; **, $p<0.001$ compared to baseline value; Å, $p<0.05$ compared to the corresponding control group. ÅÅ, $p<0.001$ compared to the corresponding control group.

aortic cross-clamping in a rat model.[6] On the contrary, De Lasson *et al.* found that dopamine at the dose of 3 $\mu g\,kg^{-1}\,min^{-1}$ administered to humans undergoing infrarenal aortic surgery improved intraoperative hemodynamic effects.[1] However, the presence of thoracic epidural sympathetic blockade in these patients may have synergistic effects with dopamine for the improvement of haemodynamics.

Dopexamine at low dose (2 $\mu g\,kg^{-1}\,min^{-1}$) does not seem to modify significantly the haemodynamic response, as McGinley *et al.* also observed in humans undergoing infrarenal abdominal aneurysm repair surgery.[18] Dopexamine used at a high dose (8 $\mu g\,kg^{-1}\,min^{-1}$) in our study may have positive effects during cross-clamping (attenuation of the increase in MAP) but produces unwanted effects (hypotension, very low pH) during reperfusion despite the elevated cardiac output. Studer *et al.* reported similar findings when using a high dose of dopexamine (10 $\mu g\,kg^{-1}\,min^{-1}$) during supraceliac aortic cross-clamping in a rat model.[6]

Obviously, further investigation is needed. It would be interesting to investigate the role of these doses of dopexamine in humans submitted to aortic aneurysm repair surgery. The possible positive impact of dopexamine in patients' outcome could give a prospective for its use in clinical practice.

In conclusion dopexamine seems superior to dopamine in reducing free radical production and subsequent lipid peroxidation during reperfusion after supraceliac aortic cross-clamping in pigs, since, it was found to reduce MDA levels after reperfusion, even when it was used in the low dose of 2 $\mu g\,kg^{-1}\,min^{-1}$.

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